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An epidemic of proteinuria in Pima Indians with Type 2 diabetes mellitus

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An epidemic of proteinuria in Pima Indians with Type 2 diabetes mellitus.

Background. The risk of proteinuria in Type 1 diabetes declined ≥30% over the past 50 years, and improvements in metabolic control are believed to be largely responsible. Little is known about secular changes in the risk of proteinuria in Type 2 diabetes.

Methods. We examined trends in the incidence rate of proteinuria in Pima Indians ≥20 years of age with diabetes diagnosed between January 1, 1955 and December 31, 1994.

Results. Among 1305 initially non-proteinuric diabetic subjects, 433 developed proteinuria during a median follow-up of 8.0 years (range 0.8 to 30.2 years). With subjects with diabetes diagnosed between 1955 and 1964 serving as the reference group, the rate of proteinuria was similar (rate ratio 1.0; 95% confidence interval, 0.79 to 1.3) in the cohort diagnosed between 1965 and 1974, 1.5 times as high (95% confidence interval, 1.1 to 2.0) in the cohort diagnosed between 1975 and 1984, and 1.9 times as high (95% confidence interval, 1.1 to 3.0) in the cohort diagnosed between 1985 and 1994, after adjusting for potential confounders in a generalized additive proportional hazards model. Between the first and last cohorts, plasma glucose concentration declined, on average, by 17% ($P = 0.0001$) and the mean arterial pressure declined by 11% ($P = 0.0001$).

Conclusions. The incidence rate of proteinuria in Pima Indians with Type 2 diabetes increased nearly twofold in the last 40 years, despite improvements in plasma glucose and blood pressure. Rapidly changing environmental or behavioral factors must play an important role in the pathogenesis of diabetic renal disease in this population.

Changes in attitudes towards metabolic regulation, the introduction of purified insulin preparations, and the widespread use of blood glucose monitoring are believed to be largely responsible for a 30 to 50% decline in the risk of proteinuria among patients diagnosed with Type 1 diabetes in the 1940s and 1950s compared to those diagnosed in the 1930s [1–3]. More aggressive glycemic control in recent years contributed to a further decline in some populations. Bojestig and coworkers reported that the 25-year cumulative incidence of proteinuria declined from 30% in patients diagnosed with diabetes between 1961 and 1965 to 9% in those diagnosed between 1966 and 1970 [4]. The level of glycemic control achieved in these patients improved during the 1980s, to become equivalent to that found in subjects receiving intensive treatment in the Stockholm Diabetes Intervention Study [5] and the Diabetes Control and Complications Trial (DCCT) [6]. The delivery of intensive management, however, presents major practical challenges, and in clinics where optimal glycemic control was not achieved, the incidence rate of proteinuria remained unchanged in patients diagnosed with diabetes after 1965 [7, 8].

Secular changes in the incidence rate of proteinuria are not described as extensively in Type 2 diabetes. Ballard and coworkers reported that the rate of proteinuria in the mostly Caucasian subjects of Rochester, Minnesota was unchanged in those with diabetes diagnosed between 1945 and 1969, despite a decline in the rate of retinopathy in the same cohort that might be attributable to improvements in diabetes care [9, 10]. They suggested that changes in the incidence rate of proteinuria attributable to diabetes may be difficult to identify in Type 2 diabetes because these patients are typically older than those with Type 1 diabetes, and so they are more prone to have diseases other than diabetes that cause proteinuria [9].

In Pima Indians, Type 2 diabetes characteristically develops at an earlier age than in Caucasians [11], and nearly all of the renal disease is attributable to diabetes [12–14]. In addition, frequent oral glucose tolerance testing of most members of the population over the past 32 years permits the onset and duration of diabetes to be determined with greater certainty than in most populations [15]. Consequently, trends in the incidence rate of proteinuria attributable to Type 2 diabetes are less likely to be obscured by

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other causes of proteinuria and by inaccuracies in estimating the onset of diabetes. The present study examines trends in the incidence rate of proteinuria in Pima Indians with Type 2 diabetes.

METHODS

Subjects

Pima and the closely related Tohono O'odham Indians from the Gila River Indian Community participate in a longitudinal diabetes study [15]. Since 1965, each member of the Community who is five years old or more is asked to have a research examination every two years. These examinations include a glucose tolerance test with determination of the glucose concentration in venous plasma drawn after an overnight fast and two hours after a 75 g oral carbohydrate load. Diabetes was defined according to criteria of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [16]. The date of diagnosis was determined from the research examinations, or from review of clinical records if diabetes was diagnosed in the course of routine medical care.

Urine specimens collected at the end of the two-hour glucose tolerance test are tested for protein by dipstick (Labstix; Ames Co., Elkhart, IN, USA). Those containing at least a trace of protein are tested quantitatively for total protein by the Shevky-Stafford method [17]. Creatinine concentration is measured in the same specimen using a modification of the picrate method of Jaffe [18], and a urinary protein-to-creatinine ratio (g protein/g creatinine) is computed. The creatinine concentration was measured at the endpoint of the creatinine-picrate reaction until July 1992 when it was replaced by a kinetic method. Proteinuria was defined as a protein-to-creatinine ratio of at least 0.5 g/g, equivalent to a total protein excretion rate of approximately 500 mg or more per day [19–21]. The date of onset of proteinuria was considered to be the midpoint between the date of the first research examination after the onset of diabetes at which proteinuria was identified and the date of the previous diabetic examination.

Arterial blood pressure was measured once in the right arm by a physician or nurse practitioner using a mercury sphygmomanometer equipped with a large adult cuff with the subject resting in the supine position. Systolic and diastolic blood pressures were recorded to the nearest 2 mm Hg, and diastolic pressure was measured at the fourth Korotkoff sound. Mean arterial blood pressure was calculated as the diastolic pressure plus one-third of the pulse pressure.

The study population included 1305 non-proteinuric Pima and Tohono O'odham Indians $\geq$20 years old with Type 2 diabetes who had two or more research examinations and were diagnosed with diabetes between January 1, 1955 and December 31, 1994. Subjects diagnosed between 1955 and 1964 were all diagnosed in the course of routine medical care, since the longitudinal research study did not start until 1965.

Statistical analysis

Incidence rates of proteinuria were calculated as the number of subjects who developed proteinuria divided by the person-years of follow-up, and expressed per 1000/year. The period of risk extended from the date of the first examination after the onset of diabetes to the date of onset of proteinuria or, if the subject had not developed proteinuria, to the date of the last examination. One hundred eighty-four subjects with proteinuria at their first examination at which they had diabetes were not included in the study. Person-time was accumulated for each subject between research examinations, and time-dependent changes in covariate values were taken into account.

Cumulative incidence was calculated from the incidence rates for each interval of diabetes duration. These cumulative incidences represent the proportions of subjects who would have proteinuria at the end of each interval of diabetes duration if there were no spontaneous remission of proteinuria, no selective mortality, and the duration-specific incidence rates of proteinuria were constant throughout the follow-up period. The cumulative incidence and its standard error at the end of each interval were estimated, assuming that the observations in each interval were independent of those in the previous intervals [22]. The variances of the duration-specific estimates were cumulated to derive the variances of the cumulative incidences [23].

Subjects were divided into four groups according to the calendar year of diabetes diagnosis; 1955 to 1964, 1965 to 1974, 1975 to 1984, and 1985 to 1994. Mean values for two-hour post-load plasma glucose concentration, mean arterial pressure, body mass index, and serum cholesterol concentration in each cohort were computed at the first examination after the onset of diabetes by analysis of covariance, after setting the values of the covariates (age, sex, and duration of diabetes) to the sample means. In subjects diagnosed between 1955 and 1964, the first examination occurred several years after the onset of diabetes, since the longitudinal research study did not start until 1965.

The secular change in the risk of proteinuria was examined using a Cox proportional hazards model to control for the effects of potentially confounding variables. These variables included age, sex, duration of diabetes, two-hour post-load plasma glucose concentration, mean arterial blood pressure, serum cholesterol concentration, body mass index, and treatment with oral hypoglycemic medicines or insulin. One subject with missing data for some of these variables at the baseline examination was not included in the study. The proportional hazards model is expressed in terms of the hazard (incidence rate)

$$h(t|x_{il},\ldots, x_{ip})$$

defined as the probability that an individual with covariates $x_{il}, \ldots, x_{ip}$ develops proteinuria in a short time interval after time (t), given survival to time t. The (linear) proportional hazards model expresses the hazard rate as

$$h(t|x_{il},\ldots, x_{ip}) = h_0(t) \exp \sum_{j=1}^{p} \beta_j x_{ij}$$

where $h_0(t)$ is an unspecified baseline hazard function. Since the secular trend in the rate of proteinuria–and other covariates–may be described more accurately by a non-loglinear relationship, a generalized additive proportional hazards model was used in the present analyses. This model relaxes the linearity assumptions and allows smooth non-linear functions of the covariates to be included in the log hazard ratio. The generalized additive proportional hazards model has the form

$$h(t|x_{il},\ldots, x_{ip}) = h_0(t) \exp \sum_{j=1}^{p} f_j x_{ij}$$

where the f_j's are smooth functions. Each f_j is estimated in a flexible manner using scatterplot smoothers [24, 25]. This modeling approach is capable of handling both linear and smoothed terms. A smoothed term was used for the duration of diabetes, but not for age, mean arterial pressure, two-hour post-load plasma glucose concentration, serum cholesterol concentration, or body mass index, since inspection of additive function plots and statistical testing of the nonlinearity of effect suggested that only duration had an important non-loglinear association with the outcome. The date of onset of diabetes was included as a smoothed term so its relationship with the outcome could be examined without the loglinear constraints imposed by conventional proportional hazards analysis. Continuous variables included in the regression models were centered at their mean baseline values, and categorical variables, with the exception of the decade of diabetes diagnosis, were coded so that the largest category was the reference group. The decade from 1955 to 1964 served as the reference category for this group of variables. If values for variables changed at subsequent examinations, the new values were included for the appropriate time periods. Product terms of predictor variables did not improve the regression models and were not included.

RESULTS

Of 1305 non-proteinuric diabetic subjects (487 men, 818 women) ≥20 years of age, 433 (149 men, 284 women) developed proteinuria during a median follow-up of 8.0 years (range = 0.8 to 30.2 years). At the baseline examination, 318 subjects (25%) were treated with antihypertensive medicines; data on antihypertensive medicines were missing in 26 subjects. Clinical and demographic features of the study population are shown in Table 1.

Table 1. Baseline clinical and demographic features of the 1305 Pima Indians (487 men, 818 women) in the study population

	Mean (SD)	Range
Age *years*	42 (13)	20–88
Duration of diabetes *years*	2.0 (3.3)	0–22.9
Body mass index kg/m^2		
Men	33 (7)	19–84
Women	36 (7)	20–73
Mean arterial pressure *mm Hg*	97 (14)	51–159
Two-hour plasma glucose *mg/dl*	316 (125)	77–1150
Serum cholesterol *mg/dl*	181 (38)	78–422

Incidence rates of proteinuria are presented in Table 2 according to age and sex. In general, the incidence rate was higher in the older subjects and similar in men and women, although there was a tendency for the rate in subjects <50 years of age to be higher in the men and in those ≥50 years of age to be higher in the women. The incidence rate rose with increasing duration of diabetes, from 10.4 per 1000/year in the first five years of diabetes to 144 per 1000/year after 25 to 29 years of diabetes (Fig. 1). The predicted cumulative incidence was 17% (95% confidence interval, 14 to 19) after 10 years, 60% (95% confidence interval, 56 to 64) after 20 years, and 87% (95% confidence interval, 80 to 92) after 30 years of diabetes duration (Fig. 2).

Figure 3 shows the incidence rate of proteinuria according to duration of diabetes and the decade in which diabetes was diagnosed. Among the subjects diagnosed with diabetes during the longitudinal research study period (1965–1994), those with the most recent onset of diabetes (1985–1994) had the highest duration-specific incidence rates of proteinuria. Subjects diagnosed prior to the start of routine glucose tolerance testing (1955–1964), who were diagnosed in the course of medical care, had duration-specific incidence rates similar to those in subjects diagnosed between 1965 and 1974.

Mean values for two-hour post-load plasma glucose concentration, mean arterial pressure, body mass index, and serum cholesterol concentration in each cohort at the first examination after the onset of diabetes are shown in Table 3, adjusting for age, sex, and duration of diabetes. In general, the two-hour post-load plasma glucose concentration, the mean arterial pressure, and the serum cholesterol concentration were lower, and the degree of obesity was higher in successive cohorts. Between the first and last cohorts, the two-hour post-load plasma glucose concentration declined, on average, by 17% from 363 mg/dl to 303 mg/dl ($P = 0.0001$), mean arterial pressure by 11% from 104 mm Hg to 93 mm Hg ($P = 0.0001$), and serum cholesterol concentration by 7% from 194 mg/dl to 181

Table 2. Number of cases and incidence rates (per 1000/year) of proteinuria, by age and sex, in Pima Indians with Type 2 diabetes

	Men			Women		
Age *years*	Cases	Person-years	Incidence rate	Cases	Person-years	Incidence rate
20–29	8	373.3	21	12	631.7	19
30–39	31	1,005.8	31	32	1,635.5	20
40–49	54	1,219.1	44	71	2,117.7	34
50–59	25	826.9	30	84	1,981.2	42
60–69	22	496.8	44	69	1,149.7	60
≥70	9	223.3	40	16	345.0	46
Total	149	4,145.2	36	284	7,860.8	36

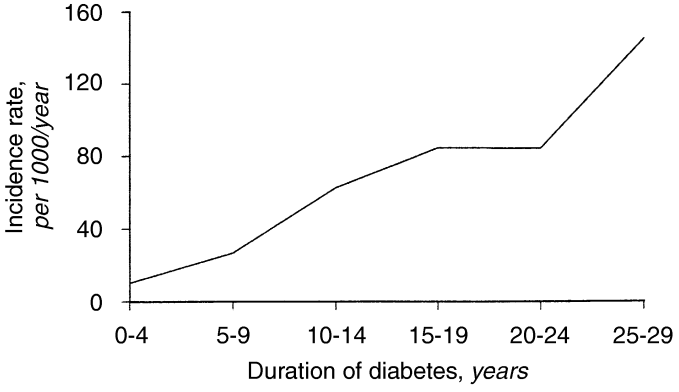

Fig. 1. Incidence rate (per 1000/year) of proteinuria in Pima Indians ≥20 years of age according to the duration of diabetes.

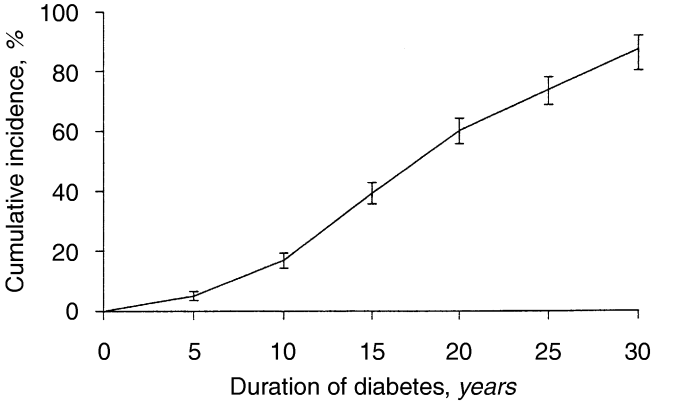

Fig. 2. Cumulative incidence (%) and 95% confidence interval of proteinuria in Pima Indians ≥20 years of age according to the duration of diabetes.

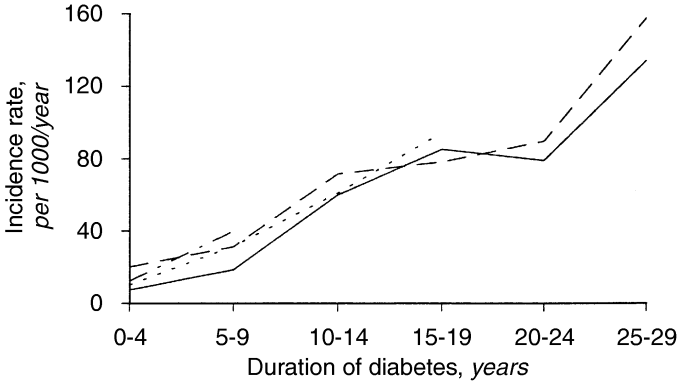

Fig. 3. Incidence rate (per 1000/year) of proteinuria in Pima Indians ≥20 years of age according to duration of diabetes and the date of onset of diabetes: 1955 to 1964 (- - -), 1965 to 1974 (–), 1975 to 1984(—), and 1985 to 1994 (— - —).

mg/dl ($P = 0.002$). The body mass index increased by 13% from 32.2 kg/m^2 to 36.5 kg/m^2 ($P = 0.0001$).

When examined as a continuous variable in a generalized additive proportional hazards model, the date of onset of diabetes was strongly associated with the incidence rate of proteinuria ($P = 0.005$), adjusting for age, sex, duration of diabetes, mean arterial pressure, two-hour plasma glucose concentration, body mass index, serum cholesterol concentration, and treatment with oral hypoglycemic medicines or insulin. The rate of proteinuria appears to have declined slightly in those diagnosed with diabetes in the late 1950s and early 1960s, but increased steadily thereafter (Fig. 4A). With subjects diagnosed between 1955 and 1964 serving as the reference group, the rate of proteinuria was similar (rate ratio 1.0; 95% confidence interval, 0.79 to 1.3) in those diagnosed between 1965 and 1974, 1.5 times as high (95% confidence interval, 1.1 to 2.0) in those diagnosed between 1975 and 1984, and 1.9 times as high (95% confidence interval, 1.1 to 3.0) in those diagnosed between 1985 and 1994 (Table 4). The incidence rate of proteinuria also increased rapidly with increasing duration of diabetes until after about 15 years of diabetes (Fig. 4B).

DISCUSSION

Pima Indians with Type 2 diabetes are extraordinarily susceptible to diabetic renal disease. Unlike Type 1 diabetes, in which the incidence rate of proteinuria increases initially and then declines after about 15 years of diabetes [2, 26, 27], the incidence rate in this population did not decline through 30 years of diabetes duration. The predicted cumulative incidence of proteinuria after 30 years of diabetes was 87%, suggesting that most diabetic Pima Indians will eventually develop renal disease if they do not first die of another disease. Even so, the cumulative incidence may underestimate the risk in the latter part of the

Table 3. Age-sex-duration adjusted mean values[a] (SE) for two-hour post-load plasma glucose concentration, mean arterial pressure, body mass index, and serum cholesterol concentration at the first examination after the onset of diabetes

Cohort	*N*	Two-hour plasma glucose *mg/dl*	Mean arterial pressure *mm Hg*	Serum cholesterol *mg/dl*	Body mass index kg/m^2
1955–64	195	363 (10)	104 (1)	194 (3)	32.2 (0.5)
1965–74	441	327 (6)	100 (1)	184 (2)	33.4 (0.3)
1975–84	383	298 (6)	94 (1)	177 (2)	34.3 (0.3)
1985–94	286	305 (7)	93 (1)	181 (2)	36.5 (0.4)

Subjects are divided into four groups according to the calendar year of diabetes diagnosis.
[a] Analysis of covariance; values for age, sex, and duration of diabetes were set to the sample means.

study, because it is calculated from the duration-specific incidence rates under the assumption that these rates were constant throughout the follow-up period. The incidence rate of proteinuria, however, increased during the time interval of the study. The risk of proteinuria was nearly two times as high in subjects diagnosed with diabetes after 1985 than in those diagnosed between 1955 and 1964. The increasing rate is not due to a declining death rate, since the overall death rate in the Pima Indians is unchanged [28]. The rising death rate from ischemic heart disease in this population [28] would probably not affect the changes in the incidence rate of proteinuria, as ischemic heart disease typically occurs after the development of proteinuria. A secular increase in the incidence rate of proteinuria of this extent has not been reported previously in patients with Type 2 diabetes. Although genetic factors may enhance the susceptibility to renal disease in Type 2 diabetes [29–31], the magnitude of the change over a span of only 40 years suggests that powerful nongenetic forces are involved.

Hyperglycemia and blood pressure are well-recognized risk factors for proteinuria in Type 2 diabetes, both in the Pima Indians [32, 33] and in other populations [9, 34]. In addition, hyperlipidemia is implicated in the development and progression of diabetic renal disease [35–38]. Each of these factors is positively related to the development of proteinuria in the present study (Table 4), but they do not explain the rising incidence rate of proteinuria, since the initial plasma glucose concentration, mean arterial pressure, and serum cholesterol concentration after the onset of diabetes were, on average, lower in subjects diagnosed with diabetes more recently than in those diagnosed in earlier years (Table 3). Moreover, unlike the majority of subjects diagnosed with diabetes during the study period (1965–1994) those diagnosed prior to the start of routine glucose tolerance testing (1955–1964) had the benefit of several years of diabetes care before these variables were measured at a research examination, so improvements in glucose and blood pressure at the onset of diabetes may be even greater than the results suggest. Therefore, other factors must be considered to explain the rising incidence rate of proteinuria found in this study.

Substantial changes in physical activity and dietary patterns may have occurred in the population during the study period, since the body mass index in subjects diagnosed with diabetes after 1985 was 13% higher, on average, than in those diagnosed prior to 1965. Changes in obesity in the study cohort are consistent with trends in the Pima population as a whole [39], which has experienced a dramatic increase in the degree of obesity since the turn of the century. Over the same period, the traditional Pima diet of grains, squash, melons and legumes, supplemented by gathered desert plants [40, 41] has evolved to a diet distributed among the major nutrients in proportions similar to the typical United States diet [42]. Studies in experimental animals suggest that long-term high-protein diets accelerate structural and functional injury within the kidney, whereas low protein diets offer renoprotection [43–45]. Moreover, morbid obesity may itself lead to proteinuria, glomerular hypertrophy, and focal and segmental glomerular sclerosis [46–48]. Although the roles of diet and exercise in the changing incidence rate of proteinuria in this population have not been assessed, obesity, as judged by the body mass index, was not a risk factor for proteinuria (Table 4). This suggests that obesity, and changes in diet and exercise that influence the degree of obesity are not primarily responsible for the dramatic secular changes that were observed.

Intrauterine exposure to diabetes increases the risk that the offspring will develop diabetes before they reach the childbearing years [49]. Pettitt and Knowler proposed that this relationship leads to a vicious cycle in which each successive generation has a higher risk of having diabetes by the time it reaches childbearing age than the preceding generation [50]. We found recently that the risk of elevated urinary albumin excretion is nearly four times as high in diabetic Pima Indians exposed to diabetes *in utero* than in those who were not exposed [51]. Although the effect of exposure to diabetes *in utero* on the fetal kidney has not been studied, it is possible that the rise in the incidence rate of renal disease seen in the present study is due, at least in part, to an increasing frequency of diabetic pregnancies in successive generations. In patients who already possess an underlying susceptibility to diabetic renal disease, a fuel-mediated teratogenic effect [52] of exposure to diabetes *in utero* may lead to earlier development of renal disease and more rapid progression of disease in adulthood once diabetes develops. Perhaps this exposure impairs nephron development, leading to a reduction in the glomerular

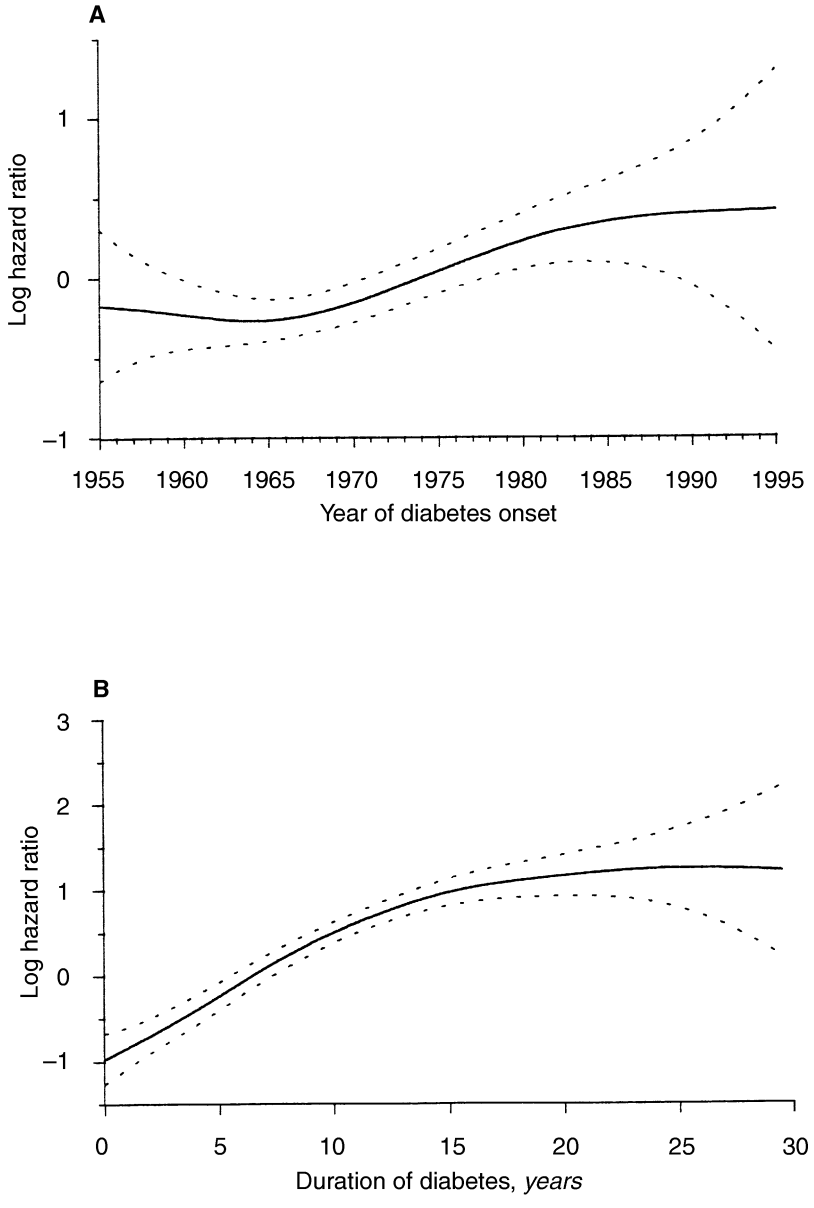

Fig. 4. Function plots for the effect of smoothed terms (*A*) year of onset and (*B*) duration of diabetes on the incidence rate of proteinuria in the additive proportional hazards model. Each curve is centered to have an average of zero over the range of the data. The dashed lines indicate approximate pointwise 95% confidence intervals.

surface area available for filtration. The extent to which intrauterine exposure to diabetes is responsible for the increasing incidence rate of proteinuria in this population, however, cannot be determined, because data on maternal diabetes during pregnancy over several generations are not available.

A slight male preponderance in the risk of proteinuria was found in the present study, in keeping with a slightly higher risk of diabetic end-stage renal disease in Pima men [12]. In addition, treatment with either oral hypoglycemic medicines or insulin was associated with a substantial increase in the risk of proteinuria, presumably reflecting the increased severity of diabetes in subjects receiving these medicines or possibly an adverse effect of diabetes treatment on the kidney.

Systematic oral glucose tolerance tests performed throughout the study permit us to identify the onset and duration of Type 2 diabetes with a degree of certainty not found in other studies. The estimates of duration, however, are less accurate in subjects examined infrequently than in those seen every two years. In addition, the duration of diabetes is more likely to be underestimated in subjects diagnosed in the course of routine medical care before 1965 and in those first diagnosed at their initial research examination, because they do not have research examinations prior to the one at which they were diagnosed with diabetes. Given the strong association between diabetes duration and the incidence rate of proteinuria, an underestimate of the duration of diabetes will result in an overestimate of the incidence rate of proteinuria for a given duration of

Table 4. Estimated adjusted effects (rate ratios and 95% confidence intervals) of the decade of diabetes diagnosis and other factors on the risk of proteinuria: results of generalized additive proportional hazards regression analysis

Model covariates	Rate ratio[a]	95% confidence interval	*P* value
Age *per* 10 *years*	1.0	0.93 to 1.1	0.71
Sex *male/female*	1.3	1.0 to 1.6	0.02
Two-hour plasma glucose *per 100 mg/dl*	1.3	1.1 to 1.4	<0.001
Mean arterial pressure *per 20 mm Hg*	1.2	1.0 to 1.4	0.01
Serum cholesterol *per 50 mg/dl*	1.0	0.92 to 1.2	0.50
Body mass index *per 5 kg/m*^{2}	0.99	0.91 to 1.1	0.76
Treatment with oral diabetes drugs *yes/no*	1.3	1.1 to 1.7	<0.001
Treatment with insulin *yes/no*	2.4	1.9 to 3.2	0.02
Decade of diabetes diagnosis			
1955–64[b]	1.0	—	—
1965–74	1.0	0.79 to 1.3	0.86
1975–84	1.5	1.1 to 2.0	0.01
1985–94	1.9	1.1 to 3.0	0.01

Due to nonlinearities in the effect of diabetes duration ($P = 0.0003$; test for nonlinearity), a smoothed term was used for duration and a rate ratio was not computed.

[a] Rate ratio for the number of units shown in parentheses

[b] Reference category

diabetes. Since the degree of misclassification of diabetes duration is likely to be greater in subjects diagnosed during the first part of the study, this misclassification would tend to reduce the secular difference in duration-specific rates. An analysis limited to the 591 subjects in whom the duration of diabetes was known with greatest certainty–those with a nondiabetic examination within five years of the one at which diabetes was diagnosed–shows the same increasing secular trend in the incidence rate of proteinuria as in the larger cohort (data not shown), suggesting that the extent of misclassification of diabetes onset and duration introduced by variability in the frequency of examinations is small. Nevertheless, since proteinuria was also determined at the research examinations, variability in the frequency of examination and loss to follow-up could lead to either an underestimate or an overestimate of changes in the incidence rate of proteinuria.

Pima Indians who chose not to participate in the research examinations may have a different incidence rate of proteinuria than those who volunteered. Quantitative measures of proteinuria are not consistently available in the clinical records, so it was not possible to estimate the incidence rate in the non-participants. However, patients who progress to end-stage renal disease are identified independently of research clinic attendance, and the incidence rate of diabetic end-stage renal disease, internally standardized for age, sex, and duration of diabetes, was similar in those examined only once (and thus excluded from the present study) and in those examined more often (data not shown), suggesting that if subjects with frequent examinations have different rates of renal disease than those who have infrequent or no examinations, the magnitude of the difference is small.

In conclusion, the incidence rate of proteinuria in diabetic Pima Indians is increasing despite improvements in plasma glucose and blood pressure. This contrasts sharply with the declining incidence rate reported in Type 1 diabetes, which is attributable, in large part, to improvements in glycemic control. If this trend is also occurring in other Type 2 diabetic populations, the public health implications are profound. Given the rising incidence rate of Type 2 diabetes worldwide, and its early age at onset in many ethnic groups, the potential importance of the intrauterine environment in enhancing the risk of renal disease in this Type of diabetes should not be overlooked.

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